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Original Article

Microbiology Section

Diagnostic Utility of Hepatitis C Core Antigen Testing for Confirmation of Active Hepatitis C Infection: A Retrospective Observational Study

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ABSTRACT

Introduction: Hepatitis C Virus (HCV) infection is one of the leading causes of chronic liver disease and a global public health problem, particularly in resource-poor countries. Elimination of HCV requires prompt testing and treatment of infected cases. Anti-HCV antibody (anti-HCV Ab) is commonly used for testing, but, due to its low positive predictive value for active infection, additional detection of HCV Ribonucleic Acid (RNA) is required to confirm HCV infection status.

Aim: To evaluate the HCV Core Antigen (HCVcAg) test as an alternative to HCV RNA detection for confirmation of active HCV infection.

Materials and Methods: This was a retrospective observational study conducted in St. John's Medical College Hospital, Bangalore, Karnataka, India from July 2021 to December 2021, on 75 leftover plasma samples which were already been tested for the HCV RNA. Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) was employed to test for HCV RNA, and the HCVcAg test was performed using Chemiluminescent Microparticle Immunoassay (CMIA) on leftover samples with a minimum volume of 700 µL. Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 25.0 and the Receiver Operating Characteristic (ROC) curve, was plotted using Python software version 3.12. Correlation between different parameters was calculated by the Spearman Rho test and the Mann-Whitney U test. A p-value <0.05 was considered statistically significant.

Results: The study comprised 75 patients aged 11 to 96 years, with the largest proportion (20, 26.67%) in the 41-50 years age group. The sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and accuracy for HCVcAg compared to HCV RNA were 83.33%, 100%, 100%, 82.50% and 90.67%, respectively. Based on ROC curve analysis, the Area Under the Curve (AUC) for HCVcAg was 0.926 (95% confidence interval, 0.863-0.989), and the cut-off value was 3.32 fmol/L. There was a significant correlation (ρ=0.890, p-value <0.001) between the quantitative values of HCVcAg and HCV RNA.

Conclusion: Prompt testing and treatment of infected individuals are critical for the elimination of Hepatitis C infection. HCVcAg has emerged as a potential alternative to HCV RNA testing for confirming active infection. It is cost-effective, technically simpler, and minimises diagnostic delays associated with molecular confirmation.

Keywords: Chemiluminescent microparticle immunoassay, Hepatitis C ribonucleic acid, Hepatitis C virus

INTRODUCTION

The HCV is a serious cause of liver disease and a major cause of morbidity and mortality worldwide, for which no prophylactic vaccine is available. HCV belongs to the family *Flaviviridae*, genus Hepacivirus, and has a positive-sense single-stranded RNA genome. It is one of the major hepatotropic viruses causing acute to chronic liver disease, leading to liver cirrhosis and hepatocellular carcinoma; routes of transmission include parenteral, sexual, and perinatal exposure [1].

Though the acute HCV infections are usually asymptomatic and mostly not associated with any life-threatening disease, the fact that around 70% (55-85%) develop chronic HCV infection is of concern. Of those with chronic HCV infection, the risk of cirrhosis ranges from 15% to 30% within 20 years. As per the World Health Organisation (WHO), an estimated 50 million people have chronic HCV infection around the world, with 1.0 million new infections occurring per year [2]. In India, 6 to 12 million people are chronically infected with HCV as per the latest estimates [3]. Therefore, timely diagnosis and prompt initiation of treatment are crucial in preventing progression to chronic stages.

To identify people infected with the virus, the current guidelines recommend testing for anti-HCV antibodies (anti-HCV Ab) using a serological test. If this is positive, a nucleic acid test for HCV RNA is required to confirm chronic infection and the need for treatment. This is important because 30% of people infected with HCV spontaneously clear the infection through a strong immune response, eliminating the need for treatment. Although no longer infected, they may still test positive for anti-HCV Ab [2,4]. Therefore, due to the low reliability of the anti-HCV Ab test in detecting active cases [5,6], further confirmation by molecular tests for HCV RNA detection is required, which is time-consuming and costly [7].

The HCV core antigen (HCVcAg) test is a potential alternative for diagnosing HCV infection. HCVcAg exists in both complete HCV virions and RNA-free core protein structures, and it is considered a surrogate marker of viral replication. HCVcAg is present in serum and plasma before detectable anti-HCV Ab, making it a good candidate surrogate for the detection of both acute and chronic HCV infections [8]. According to previously published studies, the HCVcAg test has a sensitivity of 80 to 99% and a specificity of >98% for the diagnosis of HCV infection [5,9]. It helps in early detection of the infection as compared to the antibody test, shortening the window period required for seroconversion; it gives accurate results within a short time for immediate treatment at a reasonable cost as compared to molecular assays [9]. HCVcAg quantification is a cost-effective alternative to HCV RNA for monitoring antiviral response, due to its correlation with molecular assays and ease of automation [9-11].

Although several studies have demonstrated the diagnostic utility of the HCVcAg assay, evidence from India remains limited [7-16]. Despite its reported equivalence to HCV RNA testing, the assay has not been routinely implemented in diagnostic laboratories.

In this context, the present study aimed to evaluate the performance of HCVcAg testing for confirmation of active Hepatitis C infection in the local setting, using HCV RNA as the reference standard, along with the distribution of HCVcAg results across the different levels of HCV RNA and to generate evidence to support its potential integration into routine diagnostic workflows.

MATERIALS AND METHODS

This was a retrospective observational study conducted at the Microbiology laboratory of St.John's Medical College Hospital, Bangalore, over a period of six months between July 2021 and December 2021. Institutional Ethics Committee (IEC) approval was obtained before initiation of the study (IEC Study Reference No: 247/2021) with a waiver of consent as the study was done on leftover plasma samples.

This was a time-bound study; all samples available during the study period, which satisfied the inclusion criteria, were taken into consideration. Therefore, 75 plasma samples, which were previously tested for HCV RNA, stored at -80°C for no longer than six months, were used in the study.

Inclusion criteria: Consecutive plasma samples with a minimum volume of 700 µL from patients who were found to be HCV antibody screen positive and subsequently tested for HCV RNA for confirmation were included in the study.

Exclusion criteria: Repeat samples from the same patient and samples with more than one freeze-thaw cycle were excluded from the study.

The samples were thawed to room temperature before testing for HCVcAg by CMIA methodology using the ARCHITECT SYSTEM (Model: i2000SR, Serial No: iSR63536, Make: Abbott, Ireland).

Principle and interpretation of HCVcAg: The ARCHITECT HCVcAg assay is a two-step immunoassay for the quantitative determination of core antigen of HCV using CMIA technology. Appropriate controls and calibrators were run as per the manufacturer's instructions [17]. Six calibrators (Cal), Cal A to Cal F, were run with every new lot of the test kit; a negative control, positive control level-1 and a positive control level-2, in the ranges, 0.00-2.99, 35.00-65.00, 210.00-390.00 femtomole/litre (fmol/L) were run with each batch of testing for internal quality control. Samples with concentration values ≥ 3.00 fmol/L were interpreted as 'reactive' and < 3.00 fmol/L as 'non reactive' for HCVcAg. Those with concentration values ≥ 3.00 fmol/L to < 10.00 fmol/L were retested in duplicate as per the manufacturer's instructions [17] and interpreted as 'non reactive' if both the retest values were < 3.00 fmol/L and as 'reactive' if one or both duplicates were ≥ 3.00 fmol/L (the initial value used as the final reported value).

Principle and interpretation of HCV RNA: HCV RNA was detected using the Xpert HCV Viral Load assay by CBNAAT on the GeneXpert platform (Serial No: 801511, Model: GXIV-4-D, Cepheid SAS, France).

The assay uses automated Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) on a closed platform for the quantitative detection of HCV RNA in human plasma. The assay detects and quantifies HCV genotypes 1-6 over a range of 10 to 100,000,000 IU/mL (1.0-8.0 log10 IU/mL). Each cartridge contains internal sample processing and probe check controls, which monitor adequate sample processing, reagent integrity and PCR amplification performance. Samples with detectable HCV RNA (≥10 IU/mL) were interpreted as positive for HCV RNA, whereas samples reported as "HCV not detected" by the system were interpreted as negative for HCV RNA. The assay was performed and reported according to the manufacturer's protocol [18], and instrument calibration was maintained as per laboratory quality control procedures. Sensitivity, specificity, PPV and NPV, accuracy, were calculated for HCVcAg in comparison to HCV RNA. The equations used for the calculation are [19]:

$$\text{Sensitivity}=\frac{\text{True positive}}{\text{True positive}+\text{False negative}}$$

$$\text{Specificity}=\frac{\text{True negative}}{\text{True negative}+\text{False positive}}$$

$$\text{Positive predictive value}=\frac{\text{True positive}}{\text{True positive}+\text{False positive}}$$

$$\text{Negative predictive value}=\frac{\text{True negative}}{\text{True negative}+\text{False negative}}$$

and Accuracy= (TP + TN) / (TP + TN + FP + FN).

The distribution of HCVcAg results was compared across the different levels of HCV RNA to describe its performance at low viral loads.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS Statistical version 25.0, except for the ROC curve, which was plotted using Python software version 3.12. Descriptive variables were presented as numbers, percentages, arithmetic mean, and standard deviation or median and quartiles, depending on the distribution. Sensitivity, specificity, PPV and NPV, accuracy, as well as ROC curve analysis were applied to HCVcAg in comparison to HCV RNA. Correlation between different parameters was calculated by the Spearman Rho test and the Mann-Whitney U test. The p-value < 0.05 was considered statistically significant.

RESULTS

A total of 75 patients were included in the study: 56 (74.67%) males and 19 (25.33%) females. The age of patients ranged from 11 to 96 years, with a mean±SD age of 43.91±16.37 years. The largest proportion, 20 (26.67%) of the patients, belonged to the age group of 41 to 50 years. Gastroenterology 35 (46.67%) and Nephrology 21 (28.00%) contributed to a majority of the samples [Table/Fig-1].

Category		n (%)
Age (years)	0-20	3 (4.0)
	21-30	14 (18.67)
	31-40	15 (20.0)
	41-50	20 (26.67)
	51-60	10 (13.33)
	>60	13 (17.33)
Gender	Male	56 (74.67)
	Female	19 (25.33)
Ward	Gastroenterology	35 (46.67)
	Nephrology	21 (28.0)
	General Medicine	12 (16.0)
	Others*	7 (9.33)

[Table/Fig-1]: Baseline characteristics.
*General surgery, Gynaecology, Medical oncology, Paediatrics

Among the 42 HCV RNA-positive samples, 36 were from newly diagnosed cases and six from patients already receiving treatment. Nevertheless, samples from patients on treatment were included in the final analysis, as this was a diagnostic accuracy study.

Out of the 75 samples, 68 (90.67%) were concordant by both methods, and 7 (9.33%) were discordant [Table/Fig-2]. Among the concordant samples, five samples gave HCVcAg values between 3 fmol/L to 10 fmol/L; retesting them in duplicate was performed as per manufacturer instructions, which consistently yielded positive results. This reinforces the assay's reliability at these levels.

Using [Table/Fig-2], the sensitivity, specificity, PPV, and NPV along with 95% confidence intervals were 83.33% (68.64, 93.03), 100% (89.42,100), 100% (90, 100) and 82.50% (70.56, 90.26), respectively, considering HCV RNA to be the gold standard; the accuracy was 90.67% (81.71, 96.16) [Table/Fig-3].

		HCV RNA		
		Detected, n (%)	Not detected, n (%)	Total, n (%)
HCVcAg	Positive	35 (46.67)	0	35 (46.67)
	Negative	7 (9.33)	33 (44.0)	40 (53.33)
Total, n (%)		42 (56.0)	33 (44.0)	75 (100)

[Table/Fig-2]: Summary of HCVcAg and HCV RNA results.

	HCVcAg (95% CI)
Sensitivity (Sn)	83.33% (68.64 to 93.03)
Specificity (Sp)	100% (89.42 to 100)
Positive Predictive Value (PPV)	100% (90 to 100)
Negative Predictive Value (NPV)	82.50% (70.56 to 90.26)
Accuracy	90.67% (81.71 to 96.16)

[Table/Fig-3]: Performance of HCVcAg considering HCV RNA as the gold standard. CI: Confidence interval

The results of HCVcAg were compared against the quantitative values of HCV RNA in log IU/mL. For this, the HCV RNA values were grouped as depicted in [Table/Fig-4].

HCV RNA		HCVcAg, n (%)		Total
		Positive	Negative	
Negative	<1 log IU/mL	0	33 (44)	33 (44)
Positive	<3 log IU/mL	3 (4)	5 (6.67)	8 (10.67)
	3-3.99 log IU/mL	2 (2.67)	2 (2.67)	4 (5.33)
	4-4.99 log IU/mL	9 (12)	0	9 (12)
	5-5.99 log IU/mL	10 (13.33)	0	10 (13.33)
	>6 log IU/mL	11 (14.67)	0	11 (14.67)

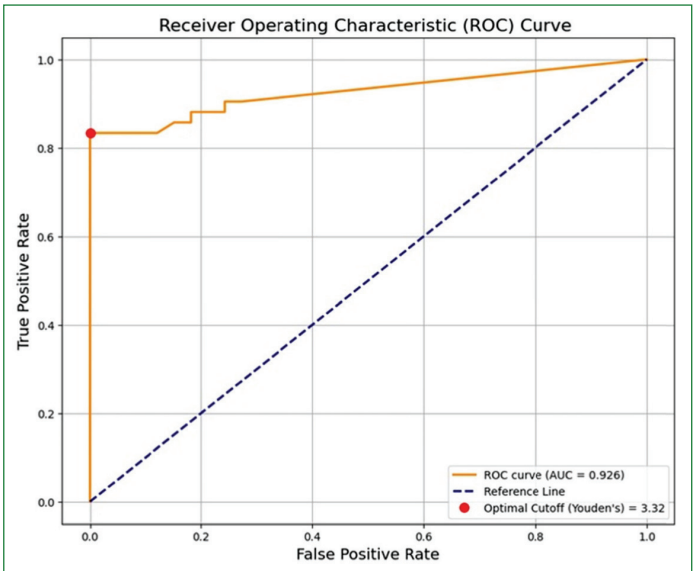
[Table/Fig-4]: Distribution of HCVcAg results across different levels of HCV RNA.

It was observed that all samples with HCV RNA ≥ 4 log IU/mL (n=30) tested positive for HCVcAg also. Out of the total HCV RNA positive samples (n=42), seven tested negative by HCVcAg; two of these samples showed HCV RNA ranging from 3-3.99 log IU/mL, and five showed <3 log IU/mL, indicating that the HCVcAg may not be detected at low HCV RNA levels [Table/Fig-4].

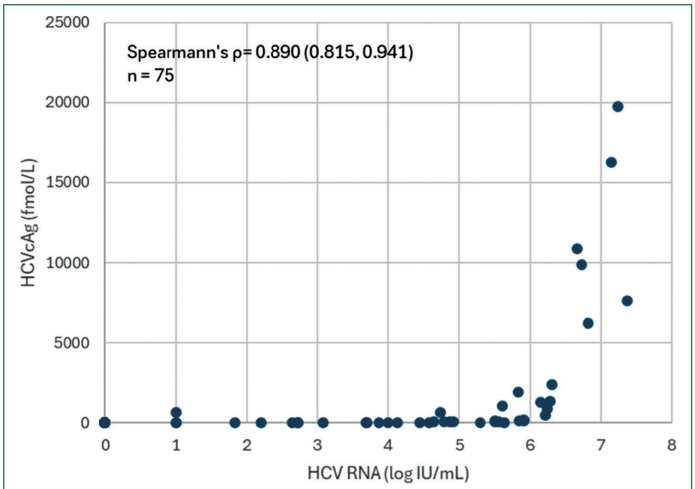
The ROC curve analysis revealed that the AUC for HCVcAg was 0.926 (95% confidence interval, 0.863-0.989) [Table/Fig-5] and the cut-off value was 3.32 fmol/L in comparison to HCV RNA as the gold standard. The sensitivity and specificity at this cut-off were 83.33% and 100%, respectively.

[Table/Fig-6] shows the scatter plot depicting the relationship between HCVcAg and HCV RNA levels. A strong positive monotonic association was observed, as indicated by a high Spearman's rank correlation coefficient (ρ=0.890; 95% CI: 0.815-0.941; n=75). This suggests that higher HCV RNA levels are consistently associated with higher HCVcAg concentrations. Although the correlation is strong, the relationship appears non linear, particularly at higher viral loads where HCVcAg levels increase disproportionately. At lower HCV RNA values, HCVcAg concentrations are clustered near zero, indicating limited sensitivity in this range. In contrast, at higher RNA levels (log IU/mL > ~6), there is a steep rise and greater dispersion in HCVcAg values, suggesting increased variability.

The liver enzymes were tested as per the clinician's request. Since this was a retrospective study, only the previously available data was analysed, hence the varying sample sizes across different liver enzymes. The levels of the liver enzymes, wherever available, were compared across the results of HCVcAg and HCV RNA. By Mann-Whitney U test, the median levels of AST and ALT were significantly higher (p-value 0.045 and 0.049, respectively) in HCV RNA positive cases as compared to the negative cases; the median levels of ALT and GGT were significantly higher (p-value 0.043 and 0.015, respectively) in HCVcAg positive cases as compared to the negative cases [Table/Fig-7].



[Table/Fig-5]: Receiver Operating Characteristic (ROC) curve analysis for diagnosing HCV infection based on HCVcAg results using HCV RNA as the gold standard.



[Table/Fig-6]: Correlation between HCVcAg (fmol/L) and HCV RNA (log IU/mL).

DISCUSSION

The HCV infection continues to impose a substantial global health burden, particularly due to its progression to chronic hepatitis, cirrhosis, and associated complications. The current diagnostic algorithm screening with anti-HCV antibodies followed by confirmation using nucleic acid testing (HCV RNA) is associated with inherent limitations, including increased turnaround time and higher costs, which may delay treatment initiation, especially in resource-limited settings [7]. Additionally, spontaneous viral clearance in a subset of patients complicates clinical decision-making regarding the need for therapy [2,4]. In this context, there is a clear need for rapid, reliable, and cost-effective assays to confirm active HCV infection.

The present study evaluated the diagnostic utility of HCVcAg in comparison with HCV RNA. The study population comprised 75 patients across a wide age range, with a predominance of males and a majority from gastroenterology and nephrology services. A subset of patients included transfusion-dependent paediatric cases, as well as individuals already receiving treatment for HCV infection, thereby reflecting a heterogeneous clinical cohort.

In this study, HCVcAg demonstrated a sensitivity of 83.33% and specificity of 100%, with corresponding PPV and NPV of 100% and

Liver Enzymes (U/L)		HCV RNA (log IU/mL)			HCVcAg (fmol/L)		
		Positive	Negative	p-value	Positive	Negative	p-value
AST (U/L)	N	36	32	0.045	30	38	0.100
	Median	54.5	29		58	34.5	
	IQR	26.2-84	14.2-59.7		25.7-87.5	16.5-60.25	
ALT (U/L)	N	36	32	0.049	30	38	0.043
	Median	42.5	24		46	26	
	IQR	24-78.7	13.5-44		23.7-87.5	18-43.5	
ALP (U/L)	N	35	30	0.216	29	36	0.182
	Median	125	91		131	91	
	IQR	91-166	71.5-205.5		94-157.5	72.2-212.5	
GGT (U/L)	N	35	30	0.081	29	36	0.015
	Median	61	39.5		62	36	
	IQR	31-101	21-89.7		38.5-121.5	21.2-70	

[Table/Fig-7]: Comparison of Liver enzyme with HCV RNA and HCVcAg results.
Abbreviations: AST: Aspartate transaminase; ALT: Alanine transaminase; ALP: Alkaline Phosphatase; GGT: Gamma glutamyl transferase; IQR: Interquartile range Mann-Whitney U test was used for the comparison between positive and negative cases

82.50%, respectively, and an overall diagnostic accuracy of 90.67%. These findings were consistent with previously published literature, where sensitivity has ranged from 80.62% to 99%, specificity from 99.12% to 100%, PPV of 100%, and NPV from 59.4% to 99.76%, with reported diagnostic accuracies of 92.20% to 95.2% [5,9,13-16, 20-22]. The high specificity (100%) and PPV (100%) observed in this study have also been reported by other studies [12,13,20] reinforcing the reliability of HCVcAg as a confirmatory test for active infection. Furthermore, a strong positive correlation between HCVcAg and HCV RNA levels was demonstrated, consistent with prior studies [5,9,13,16,21,23], thereby supporting the equivalence of HCVcAg with molecular assays in reflecting viral replication.

ROC analysis in the present study demonstrated excellent diagnostic performance of HCVcAg, indicating high discriminative ability comparable to HCV RNA. The optimal cut-off value identified was 3.32 fmol/L, which yielded the best balance between sensitivity and specificity. Comparable findings have been reported in other studies, with cut-off values of 2.82 fmol/L [15] and 31.86 fmol/L [13] likely reflecting variability in study populations and assay methodologies.

Despite its advantages, certain limitations of HCVcAg testing were evident. Discordant results between HCVcAg and HCV RNA were observed in 9.3% of cases, predominantly among patients with low-level viremia. Most of these patients had viral loads below 3 log IU/mL. Similar findings have been reported in other studies, with discordance rates of 4.3% [23] and 4.5%, [12] and reduced detection of HCVcAg at viral loads <3 log IU/mL [23]. As few as 5.3% of treatment-naive patients with chronic HCV infection generally exhibit very low viral loads <3000 IU/mL [24], indicating that the observed sensitivity of 83.33% is unlikely to significantly compromise its utility for routine diagnostic confirmation. However, in high-risk individuals who test positive for anti-HCV by routine screening but negative for HCV RNA, additional confirmation using molecular assays may be warranted.

The study also demonstrated that liver enzyme levels were significantly elevated in patients with active infection. Median AST and ALT levels were significantly higher in HCV RNA-positive cases, while ALT and GGT levels were significantly elevated in HCVcAg-positive cases. These findings are consistent with a previous study indicating that transaminase levels correlate with viral replication and may serve as surrogate markers for monitoring disease activity [25].

Limitation(s)

This study had certain limitations. As it was time-bound, the desired sample size could not be achieved, which may have affected the statistical power of the study. The inclusion of a heterogeneous patient population limited direct comparability with findings from other studies. Additionally, potential confounding factors were not adjusted for when assessing the association between liver enzyme levels and the performance of the diagnostic assays.

CONCLUSION(S)

The findings of this study support HCVcAg as a reliable alternative to HCV RNA testing for the confirmation of active HCV infection, owing to its high specificity and strong correlation with viral load. Additionally, HCVcAg offers important practical advantages, including lower cost and technical simplicity. Incorporation of this assay into routine diagnostic algorithms has the potential to reduce reliance on molecular confirmation, thereby minimising diagnostic delays. This, in turn, can facilitate earlier initiation of treatment and improve patient outcomes. Such an approach is particularly valuable in low- and middle-income settings, where access to molecular testing remains limited.

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- Manual Googling: May 04, 2026
- iThenticate Software: May 09, 2026 (16%)

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EMENDATIONS: 6

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